(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 February 2005 (17.02.2005)

PCT

(10) International Publication Number
WO 2005/013961 A1

(51) International Patent Classification[7]: A61K 31/18, A61P 25/18

(21) International Application Number: PCT/US2004/017439

(22) International Filing Date: 2 July 2004 (02.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/487,967 17 July 2003 (17.07.2003) US
60/487,966 17 July 2003 (17.07.2003) US

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,*

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(54) Title: COMBINATION THERAPY FOR TREATMENT OF COGNITIVE DISORDERS OR PSYCHOSES

(57) Abstract: The present invention provides a method for treating a patient suffering from or susceptible to psychosis, comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic and an effective amount of a second component which is an AMPA receptor potentiator, and the pharmaceutical compositions thereof. The present invention also provides a method for treating a patient suffering from or susceptible to a cognitive disorder, comprising administering to said patient an effective amount of a first component which is a drug useful in treating a cognitive disorder and an effective amount of a second component which is an AMPA receptor potentiator, and the pharmaceutical compositions thereof.

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IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

COMBINATION THERAPY FOR TREATMENT OF COGNITIVE DISORDERS OR PSYCHOSES

BACKGROUND OF THE INVENTION

Glutamate is the major excitatory neurotransmitter in the central nervous system. Three glutamate receptor ion channel subtypes have been identified based on their sensitivity to the selective activators (agonists) N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate.

AMPA receptors mediate cellular responses to glutamate by direct and indirect mechanisms. When activated by glutamate or AMPA, AMPA receptor ion channels allow sodium ions (Na^+) and calcium ions (Ca^{2+}) to pass directly through the channel pore. In addition, AMPA receptor ion channels can facilitate the activation of NMDA receptors by initiating cellular depolarization that relieves magnesium ion (Mg^{2+})-dependent block of NMDA receptors.

Multiple AMPA receptor subtypes have been identified and cloned: GluR1, GluR2, GluR3, and GluR4 as reviewed by Hollmann and Heinemann, *Ann. Rev. Neurosci.*, 17, 31-108 (1994). Each subunit consists of a sequence of approximately 900 amino acids. Four subunits are thought to assemble to form a tetrameric ion channel complex with the functional properties of this ion channel most likely being determined by its subunit composition.

Ion channel currents activated by glutamate via AMPA receptors are transient. The time course of currents is modified by refractory states caused during glutamate binding which is referred to as desensitization and by the rate of glutamate removal from the ion channel binding site which results in deactivation. Ion influx through AMPA receptors may be enhanced by compounds that either prevent desensitization or by compounds that slow deactivation rates. Compounds that enhance glutamate-stimulated ion influx at AMPA receptors are known as positive AMPA receptor allosteric modulators or AMPA receptor potentiators. One such compound, which selectively potentiates AMPA receptor function, is cyclothiazide. Since AMPA receptors play a pivotal role in mediating fast excitatory transmission in the central nervous system,

molecules that enhance AMPA receptor function have multiple therapeutic targets including the treatment of psychosis.

More specifically, for example, compounds that potentiate AMPA receptors have been shown to enhance synaptic activity *in vitro* and *in vivo* as disclosed, for example, by I. Ito, et al., *J. Physiol.*, 424, 533-543 (1990) and A. Copani, et al., *Journal of Neurochemistry*, 58, 1199-1204 (1992). Such compounds have also been shown to enhance learning and memory in rats, monkeys, and humans, and are reviewed by Gouliaev and Senning, *Brain Research Reviews*, 19, 180-222 (1994).

In addition, International Patent Application Publication WO 98/33496 published August 6, 1998 discloses certain AMPA receptor potentiators which are useful, for example, for treating psychiatric and neurological disorders, such as cognitive disorders, Alzheimer's disease, age-related dementias, age-induced memory impairment, tardive dyskinesia, Huntington's chorea, myoclonus, Parkinson's disease, reversal of drug-induced states (such as cocaine, amphetamines, alcohol-induced states), depression, attention deficit disorder, attention deficit hyperactivity disorder, psychosis, cognitive deficits associated with psychosis, and drug-induced psychosis. J.R. Kimball, et al., *Society for Neuroscience Abstracts*, 26(1-2), 528.19, 30th Annual Meeting, New Orleans, (November 4-9, 2000) disclose an orally active AMPA receptor potentiator that enhances spatial learning and memory performance in rats. In addition, United States Patent No. 6,166,008, issued December 26, 2000 discloses the combination of certain AMPA receptor up-modulators in combination with neuroleptics for the treatment of schizophrenia.

Psychoses are serious mental illnesses characterized by defective or lost contact with reality. Psychotic patients may also suffer hallucinations and delusions as part of their disease. In addition, cognitive dysfunction is often present in psychotic patients wherein, for example, the individual may be confused, disoriented, or may suffer from memory impairment. Psychoses exact a tremendous emotional and economic toll on patients, their families, and society as a whole. While the mechanisms underlying these diverse disease states are poorly understood, recently discovered therapies are offering new hope for the treatment of psychotic patients. Progress in the treatment of psychotic

conditions has been achieved through the introduction of new, atypical antipsychotic agents.

While the overall profile of atypical antipsychotics is superior to that of traditional agents (e.g. haloperidol), atypical antipsychotics only minimally reverse certain aspects of the illness, such as negative symptoms (e.g. mood and affect, cognitive dysfunction). However, AMPA receptor potentiators may be used in combination with atypical antipsychotics to enhance the antipsychotic's effectiveness at lower doses, to increase the antipsychotic's overall effectiveness against negative symptoms, or the combination may be used to ameliorate the cognitive deficits that are not sufficiently treated by antipsychotics in the treatment of psychoses, such as schizophrenia.

Certain AMPA receptor potentiators, such as 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine or {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine may be used in combination with other drugs useful in treating cognitive disorders, for example, to increase their effectiveness in treating cognitive disorders at lower doses, to reduce the anxiety or irritability often associated with cognitive disorders, to reduce side effects associated with drugs useful in treating cognitive disorders, or to ameliorate the cognitive deficits associated with certain disorders, such as multiple sclerosis. In addition, such combinations may delay institutionalization of the patient suffering from a cognitive disorder, such as Alzheimer's disease or dementia of the Alzheimer's type, or reduce the burden on the caregiver of the patient who is suffering from the cognitive disorder.

SUMMARY OF THE INVENTION

The invention provides a pharmaceutical composition which comprises a first component which is an atypical antipsychotic, and a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

The invention also provides a method for treating a patient suffering from or susceptible to psychosis, comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic and an effective amount of a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}{(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

In addition, the invention provides a method for treating a patient suffering from or susceptible to schizophrenia, comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic and an effective amount of a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

The present invention also provides the use of an atypical antipsychotic, in combination with an effective amount of a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof for the manufacture of a medicament for treating schizophrenia.

The invention also provides a pharmaceutical composition which comprises a first component, which is a drug useful in treating a cognitive disorder, and a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

The invention also provides a method for treating a patient suffering from or susceptible to a cognitive disorder, comprising administering to said patient an effective amount of a first component which is a drug useful in treating a cognitive disorder and an

effective amount of a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

The present invention also provides the use of a drug useful in treating a cognitive disorder, in combination with an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}{(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof for the manufacture of a medicament for treating a cognitive disorder.

DETAILED DESCRIPTION OF THE INVENTION

It is understood by one of ordinary skill in the art that cognition includes various "domains". These domains include short-term memory, long term memory, working memory, executive function, and attention. As used herein the term "cognitive disorder" is meant to encompass any disorder characterized by a deficit in one or more of the cognitive domains, including but not limited to short term memory, long term memory, working memory, executive function, and attention. It is further understood that the term "cognitive disorder" includes, but is not limited to the following specific disorders: age-related cognitive decline, mild cognitive impairment, Alzheimer's disease, dementia, dementia of the Alzheimer's type, Parkinson's dementia, Lewy Body dementia, substance-induced persisting dementia, alcohol-induced persisting dementia, alcohol-induced cognitive impairment, AIDS-induced dementia, learning disorders, cognitive deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage, vascular dementia, multi-infarct dementia, cognitive deficits associated with amylotrophic lateral sclerosis, and cognitive deficits associated with multiple sclerosis.

The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1994, American Psychiatric Association, Washington, D.C.) provides a diagnostic tool for identifying many of the disorders described herein. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for disorders described herein, including those as described in the DMS-IV and that terminology and classification systems evolve with medical scientific progress.

In one general expression of the present invention, the first component is a compound which is a drug useful in treating a cognitive disorder. As used herein the term "a drug useful in treating a cognitive disorder" includes, but is not limited to acetylcholinesterase inhibitors, NMDA receptor antagonists, 5-HT_6 antagonists, M1 agonists, serotonin reuptake inhibitors, norepinephrine reuptake inhibitors, combined

serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, phosphodiesterase-4 inhibitors, tricyclic antidepressants, and AMPA receptor potentiators. More specifically, the term "a drug useful in treating a cognitive disorder" includes, but is not limited to the following compounds which are well known and readily available to one of ordinary skill in the art: donepezil, rivastigmine, galantamine, memantine, tacrine, phenserine, physostigmine, xanomeline, CX516, milameline, aniracetam, piracetam, oxiracetam, suritozole, fluoxetine, sertraline, citalopram, duloxetine, atomoxetine, venlafaxine, milnacipran, fluvoxamine, paroxetine, buproprion, reboxetine, imipramine, and rolipram.

The second component is a compound which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}{(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}{(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1).

In another general expression of the present invention, the first component is a compound which acts as an atypical antipsychotic. The essential feature of an atypical antipsychotic is less acute extra pyramidal symptoms, especially dystonias, associated with therapy as compared to a typical antipsychotic such as haloperidol. Clozapine, the prototypical atypical antipsychotic, differs from the typical antipsychotics with the following characteristics: (1) greater efficacy in the treatment of overall psychopathology

in patients with schizophrenia nonresponsive to typical antipsychotics; (2) greater efficacy in the treatment of negative symptoms of schizophrenia; and (3) less frequent and quantitatively smaller increases in serum prolactin concentrations associated with therapy (Beasley, et al., *Neuropsychopharmacology*, 14(2), 111-123 , (1996)). Clozapine, 8-chloro-1-(4-methyl-1-piperazinyl)-5H-dibenzo[1,4]diazepine, is described in U.S. Patent No. 3,539,573. Atypical antipsychotics include, but are not limited to the following which are well known and readily available to one of ordinary skill in the art:

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is a known compound and is described in U.S. Patent No. 5,229,382 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis as described and claimed in U.S. Patent No. 5,229,382; a polymorph form is disclosed in U.S. Patent No. 5,736,541;

Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Patent No. 4,804,663;

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Patent No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Patent Nos. 5,112,838 and 5,238,945. U.S. Patent Nos. 4,710,500; 5,112,838; and 5,238,945;

Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,879,288, Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt; and

Ziprasidone, 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in U.S. Patent Nos. 4,831,031 and 5,312,925. Its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,831,031.

Aripiprazole, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril, is described in U.S. Patent 5,006,528.

Zotepine, 2-[(8-chlorodibenzo[b,f]thienpin-10-yl)-oxy]-N,N-dimethylethanamine, is descri in U.S. Patent No. 3,704,245.

Iloperidone, is described in U.S. Patent No. 5,364,866.

Amisulpride, 4-amino-N-[(1-ethyl-2-pyrrolidin-yl)methyl]-5-(ethylsulfonyl)-2-methoxybenzamide, is described in Belgium Patent No. 872,585 and U.S. Patent No. 4,401,822.

The second component is a compound which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

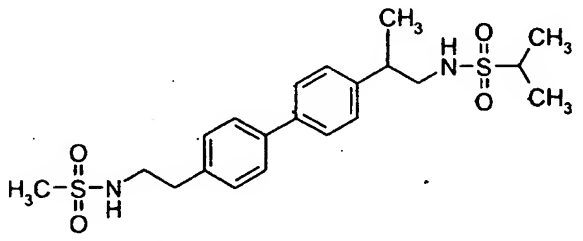
c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}{(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

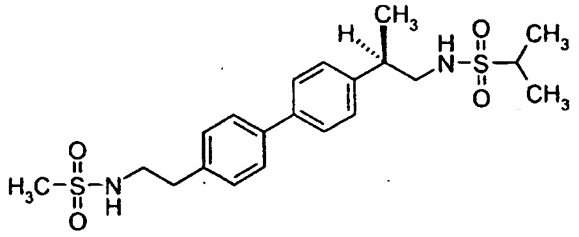
f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1).

As used herein the name "2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine" refers to the following compound:



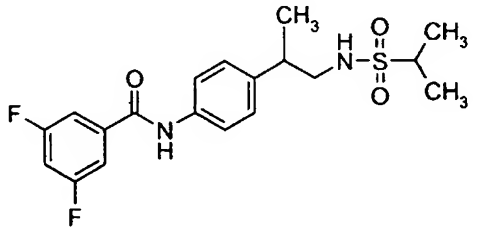
which is described in WO 98/33496 (see example 51) and WO 01/90057 and can be prepared by one of ordinary skill in the art following the procedures set forth therein.

As used herein the name "{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine" refers to the following compound:



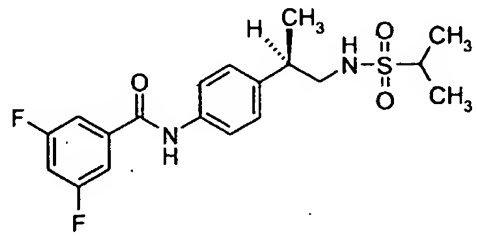
which is described in WO 01/90057 and can be prepared by one of ordinary skill in the art following the procedures set forth therein.

As used herein the name "N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide" refers to the following compound:



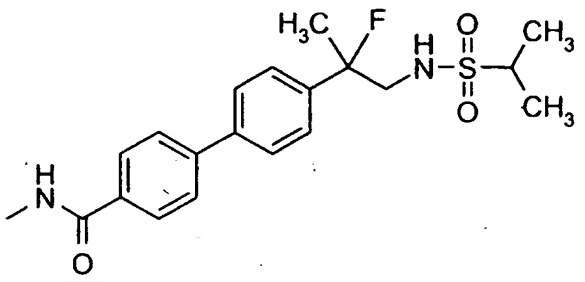
which is described in WO 01/90056 and can be prepared by one of ordinary skill in the art following the procedures set forth therein.

As used herein the name "N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide" refers to the following compound:



which is described in WO 01/90056 and can be prepared by one of ordinary skill in the art following the procedures set forth therein.

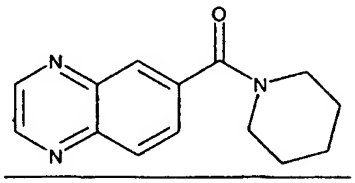
As used herein the name "{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide" refers to the following compound:



which is described in WO 00/66546 at example 11 and can be prepared by one of ordinary skill in the art following the procedures set forth therein.

As used herein the compound referred to as "{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1)" is described in WO 00/66546 at example 11a and can be prepared by one of ordinary skill in the art following the procedures set forth therein.

As used herein the term "CX516" refers to a compound of the following structure:



The ability of compounds to potentiate glutamate receptor-mediated response may be determined by one of ordinary skill in the art, for example, using fluorescent calcium indicator dyes (Molecular Probes, Eugene, Oregon, Fluo-3) and by measuring glutamate-evoked efflux of calcium into GluR4 transfected HEK293 cells, as described in more detail below.

In one test, 96 well plates containing confluent monolayers of HEK cells stably expressing human GluR4B (obtained as described in European Patent Application Publication Number EP-A1-583917) are prepared. The tissue culture medium in the wells is then discarded, and the wells are each washed once with 200 µl of buffer

(glucose, 10mM, sodium chloride, 138mM, magnesium chloride, 1mM, potassium chloride, 5mM, calcium chloride, 5mM, N-[2-hydroxyethyl]-piperazine-N-[2-ethanesulfonic acid], 10mM, to pH 7.1 to 7.3). The plates are then incubated for 60 minutes in the dark with 20 μM Fluo3-AM dye (obtained from Molecular Probes Inc., Eugene, Oregon) in buffer in each well. After the incubation, each well is washed once with 100 μl buffer, 200 μl of buffer is added and the plates are incubated for 30 minutes.

Solutions for use in the test are also prepared as follows. 30 μM, 10 μM, 3 μM and 1 μM dilutions of test compound are prepared using buffer from a 10 mM solution of test compound in DMSO. 100 μM cyclothiazide solution is prepared by adding 3 μl of 100 mM cyclothiazide to 3 ml of buffer. Control buffer solution is prepared by adding 1.5 μl DMSO to 498.5 μl of buffer.

Each test is then performed as follows. 200 μl of control buffer in each well is discarded and replaced with 45 μl of control buffer solution. A baseline fluorescent measurement is taken using a FLUOROSKAN II fluorimeter (Obtained from Labsystems, Needham Heights, MA, USA, a Division of Life Sciences International Plc). The buffer is then removed and replaced with 45 μl of buffer and 45 μl of test compound in buffer in appropriate wells. A second fluorescent reading is taken after 5 minutes incubation. 15 μl of 400 μM glutamate solution is then added to each well (final glutamate concentration 100 μM), and a third reading is taken. The activities of test compounds and cyclothiazide solutions are determined by subtracting the second from the third reading (fluorescence due to addition of glutamate in the presence or absence of test compound or cyclothiazide) and are expressed relative to enhance fluorescence produced by 100 μM cyclothiazide.

In another test, HEK293 cells stably expressing human GluR4 (obtained as described in European Patent Application Publication No. EP-A1-0583917) are used in the electro-physiological characterization of AMPA receptor potentiators. The extracellular recording solution contains (in mM): 140 NaCl, 5 KCl, 10 HEPES, 1 $MgCl_2$, 2 $CaCl_2$, 10 glucose, pH = 7.4 with NaOH, 295 mOsm kg-1. The intracellular recording solution contains (in mM): 140 CsCl, 1 $MgCl_2$, 10 HEPES, (N-[2-hydroxyethyl]piperazine-N1-[2-ethanesulfonic acid]) 10 EGTA (ethylene-bis(oxyethylene-nitrilo)tetraacetic acid), pH = 7.2 with CsOH, 295 mOsm kg-1. With

these solutions, recording pipettes have a resistance of 2-3 MΩ. Using the whole-cell voltage clamp technique (Hamill et al.(1981)Pflügers Arch., 391: 85-100), cells are voltage-clamped at -60mV and control current responses to 1 mM glutamate are evoked. Responses to 1 mM glutamate are then determined in the presence of test compound. Compounds are deemed active in this test if, at a test concentration of 10 μM, they produce a greater than 30% increase in the value of the current evoked by 1 mM glutamate.

In order to determine the potency of test compounds, the concentration of the test compound, both in the bathing solution and co-applied with glutamate, is increased in half log units until the maximum effect was seen. Data collected in this manner are fit to the Hill equation, yielding an EC_{50} value, indicative of the potency of the test compound. Reversibility of test compound activity is determined by assessing control glutamate 1mM responses. Once the control responses to the glutamate challenge are re-established, the potentiation of these responses by 100 μM cyclothiazide is determined by its inclusion in both the bathing solution and the glutamate-containing solution. In this manner, the efficacy of the test compound relative to that of cyclothiazide can be determined.

As used herein the term "potentiating glutamate receptor function" refers to any increased responsiveness of glutamate receptors, for example AMPA receptors, to glutamate or an agonist, and includes but is not limited to inhibition of rapid desensitization or deactivation of AMPA receptors to glutamate.

As used herein the term "AMPA receptor potentiator" refers to a compound which inhibits the rapid desensitization or deactivation of AMPA receptors to glutamate.

Certain combinations of atypical antipsychotics and AMPA receptor potentiators are particularly preferred, as set forth in Table I:

Table I. Particularly Preferred Combinations.

First Component	Second Component
olanzapine	N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide
olanzapine	N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-

	difluorophenyl)carboxamide
olanzapine	2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
olanzapine	{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
olanzapine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide
olanzapine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1)
risperidone	N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide
risperidone	N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide
risperidone	2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
risperidone	{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
risperidone	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide
risperidone	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1)
sertindole	N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide
sertindole	N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide
sertindole	2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
sertindole	{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
sertindole	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide
sertindole	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-

	methylcarboxamide (enantiomer 1)
quetiapine	N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide
quetiapine	N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide
quetiapine	2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
quetiapine	{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}{(methylethyl)sulfonyl]amine
quetiapine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide
quetiapine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1)
ziprasidone	N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide
ziprasidone	N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide
ziprasidone	2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
ziprasidone	{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
ziprasidone	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide
ziprasidone	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1)
aripiprazole	N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide
aripiprazole	N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide
aripiprazole	2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
aripiprazole	{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine

aripiprazole	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide
aripiprazole	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1)

Certain combinations of first (i.e., drug useful for treating a cognitive disorder and second (i.e., AMPA receptor potentiator) components are particularly preferred, as set forth in Table II.

Table II.

First Component	Second Component
donepezil	N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide
donepezil	N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide
donepezil	2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
donepezil	{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}{(methylethyl)sulfonyl]amine
donepezil	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide
donepezil	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1)
rivastigmine	N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide
rivastigmine	N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide
rivastigmine	2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}{(methylethyl)sulfonyl]amine
rivastigmine	{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
rivastigmine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-

	methylcarboxamide
rivastigmine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1)
galantamine	N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide
galantamine	N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide
galantamine	2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
galantamine	{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
galantamine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide
galantamine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1)
memantine	N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide
memantine	N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide
memantine	2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
memantine	{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}{(methylethyl)sulfonyl]amine
memantine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide
memantine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1)
tacrine	N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide
tacrine	N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide
tacrine	2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine

tacrine	{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine
tacrine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide
tacrine	{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1)

It will also be understood that while the use of a single atypical antipsychotic as a first component compound is preferred, combinations of two or more atypical antipsychotics may be used as a first component if necessary or desired. Similarly, while the use of a single AMPA receptor potentiator as a second component compound is preferred, combinations of two or more AMPA receptor potentiators may be used as a second component if necessary or desired.

It will also be understood that while the use of a single drug useful in treating a cognitive disorder as a first component compound is preferred, combinations of two or more drugs useful in treating a cognitive disorder may be used as a first component if necessary or desired. Similarly, while the use of a single AMPA receptor potentiator as a second component compound is preferred, combinations of two or more AMPA receptor potentiators may be used as a second component if necessary or desired.

It is understood by the skilled reader that many of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the present invention.

Some of the compounds used in this invention may react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-

bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, oxalic acid or fumaric acid.

Administration

The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred dosages, can and will be provided here. Dosage for some of the drugs will be given in order to create a guideline for any of the desired combinations.

Donepizil: from about 1 mg to about 20 mg, once/day; with from about 5 mg to about 10 mg, once/day being preferred.

Rivastigmine: from about 1 mg to about 15 mg daily; with from about 5 to 12 mg daily being preferred;

Galantamine: from about 4 mg to 64 mg daily; with from about 4 mg to about 32 mg daily being preferred;

Memantine: from about 5 mg to about 30 mg/kg daily, with about 20 mg daily being preferred.

Olanzapine: from about 0.25 to 50 mg, once/day; preferred, from 1 to 30 mg, once/day; most preferably 1 to 20 mg once/day, and most especially preferred 1 to 10 mg once/day;

Clozapine: from about 12.5 to 900 mg daily; preferred, from about 150 to 450 mg daily;

Risperidone: from about 0.25 to 16 mg daily; preferred from about 2-8 mg daily;

Sertindole: from about .0001 to 1.0 mg/kg daily;

Quetiapine: from about 1.0 to 40 mg/kg given once daily or in divided doses;

Ziprasidone: from about 5 to 500 mg daily; preferred from about 50 to 100 mg daily.

Aripiprazole from about 1 to about 50 mg daily, preferred from about 5 to about 30 mg daily.

N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide from about 0.1 mg to about 20 mg daily.

N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide from about 0.1 mg to about 20 mg daily.

2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine from about 0.1 mg to about 10 mg daily.

{(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine from about 0.1 mg to about 10 mg daily.

{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide from about 1 mg to about 50 mg daily.

{4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1) from about 1 mg to about 50 mg daily.

In more general terms, one would create a combination of the present invention by choosing a dosage of first and second component compounds according to the spirit of the above guideline.

The adjunctive therapy of the present invention is carried out by administering a first component together with the second component in any manner which provides effective levels of the compounds in the body at the same time. All of the compounds concerned are orally available and are normally administered orally, and so oral administration of the adjunctive combination is preferred. They may be administered together, in a single dosage form, or they may be administered separately in any sequential order or concomitantly.

However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. One of the drugs may be administered by one route, such as oral, and the others may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

The adjunctive combination may be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating both compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally usable pharmaceutical compositions are particularly preferred. Such adjunctive pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each dosage unit may contain the daily doses of both components, or may contain a fraction of the daily doses, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the component compounds, and a fraction of the dose of the other component compound. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compounds. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the adjunctive therapy is being given.

The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional, except for the presence of the combination of the present

invention. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The activity of the adjunctive combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus

pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate.

Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients. Capsules and tablets are the preferred dosage unit form.

When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

As used herein the term "psychosis" includes schizophrenia, schizophreniform diseases, mania, schizoaffective disorders, and depression with psychotic features. The above mentioned conditions represent multiple disease states. For example, schizophrenia is referred to in various forms as catatonic, disorganized, paranoid,

undifferential, and residual, among others. All the various forms of the disorders mentioned herein are contemplated as part of the present invention.

The following list further illustrates a number of these disease states, which are treated by the present combination, many of which are classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM IV): Paranoid Type Schizophrenia, Disorganized Type Schizophrenia, Catatonic Type Schizophrenia, Undifferentiated Type Schizophrenia, Residual Type Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder, Psychotic Disorder Due to a General Medical Condition, Substance-Induced Psychotic Disorder, Psychotic Disorder Not Otherwise Specified, Major Depressive Disorder with Psychotic Features, Schizoid Personality Disorder, and Schitzotypal Personality Disorder.

All of these disorders are readily diagnosed by the skilled clinician using well established criteria, including those in the DSM IV. In particular, a patient suffering from or susceptible to psychosis can be readily diagnosed using the methods described in the DSM-IV and other criteria known in the art.

As will be appreciated by the skilled person, there are alternative nomenclatures, nosologies, and classification systems for the psychoses described herein and that these systems evolve with medical scientific progress. Applicants do not intend that the present invention be limited to any disorders literally mentioned in the DSM-IV.

As used herein, the term "effective amount" refers to the amount or dose of each component, upon single or multiple dose administration to the patient, which provides the desired effect in the patient under diagnosis or treatment.

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose of compounds administered, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the

preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances. The compounds can be administered by a variety of routes, including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, bucal or intranasal routes. Alternatively, the compounds may be administered by continuous infusion.

As used herein the term "patient" refers to a mammal, such as a mouse, guinea pig, rat, dog or human. It is understood that the preferred patient is a human.

As used herein, the terms "treating" or "to treat" each mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder. As such, the methods of this invention encompass both therapeutic and prophylactic administration.

WE CLAIM:

1. A pharmaceutical composition which comprises a first component which is an atypical antipsychotic and a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

2. A pharmaceutical composition according to claim 1 wherein the atypical antipsychotic is selected from the group consisting of olanzapine, risperidone, sertindole, ziprasidone, quetiapine, iloperidone, amisulpride, and aripiprazole.

3. A pharmaceutical composition according to claim 2 wherein the atypical antipsychotic is olanzapine.

4. A pharmaceutical composition which comprises a first component which is olanzapine and a second component which is N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide.

5. A pharmaceutical composition which comprises a first component which is olanzapine and second component which is {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine.

6. A method for treating a patient suffering from or susceptible to psychosis, comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic and an effective amount of a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

7. A method for treating a patient suffering from or susceptible to schizophrenia, comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic and an effective amount of a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

8. A method according to claim 7 wherein the atypical antipsychotic is selected from the group consisting of olanzapine, risperidone, sertindole, ziprasidone, quetiapine, iloperidone, amisulpride, and aripiprazole.

9. A method according to claim 8 wherein the atypical antipsychotic is olanzapine.

10. A method for treating a patient suffering from or susceptible to schizophrenia, comprising administering to said patient an effective of a first component which is olanzapine and a second component which is N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide.

11. A method for treating a patient suffering from or susceptible to schizophrenia, comprising administering to said patient an effective of a first component which is olanzapine and second component which is {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine.

12. The use of an atypical antipsychotic, in combination with an effective amount of a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}{(methylethyl)sulfonyl}amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}{(methylethyl)sulfonyl}amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof for the manufacture of a medicament for treating psychosis.

13. A pharmaceutical composition which comprises a first component, which is a drug useful in treating a cognitive disorder, and a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

14. A pharmaceutical composition according to claim 13 wherein the first component is selected from the group consisting of an acetylcholinesterase inhibitor, an NMDA receptor antagonist, and an AMPA receptor potentiator.

15. A pharmaceutical composition according to claim 14 wherein the first component is selected from the group consisting of donepezil, rivostigmine, galantamine, and memantine.

16. A pharmaceutical composition according to claim 15 wherein the second component is {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine.

17. A method for treating a patient suffering from or susceptible to a cognitive disorder, comprising administering to said patient an effective amount of a first component which is a drug useful in treating a cognitive disorder and an effective amount of a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

18. A method for treating a patient suffering from or susceptible to Alzheimer's disease, comprising administering to said patient an effective amount of a first component which is a drug useful in treating a cognitive disorder and an effective amount of a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

19. A method for treating a patient suffering from or susceptible to dementia of the Alzheimer's type, comprising administering to said patient an effective amount of a first component which is a drug useful in treating a cognitive disorder and an effective amount of a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

20. A method for treating a patient suffering from or susceptible to mild cognitive impairment, comprising administering to said patient an effective amount of a first component which is a drug useful in treating a cognitive disorder and an effective amount

of a second component which is an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts thereof.

21. The use of a drug useful in treating a cognitive disorder, in combination with an AMPA receptor potentiator selected from the group consisting of:

a) N-2-(4-N-(3,5-difluorobenzamido)phenyl)propyl-2-propanesulfonamide;

b) N-[4-((1R)-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl](3,5-difluorophenyl)carboxamide;

c) 2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

d) {(2R)-2-[4-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)phenyl]propyl}[(methylethyl)sulfonyl]amine;

e) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide; and

f) {4-[4-(1-fluoro-1-methyl-2-{[(methylethyl)sulfonyl]amino}ethyl)phenyl]phenyl}-N-methylcarboxamide (enantiomer 1); and the pharmaceutically acceptable salts

thereof for the manufacture of a medicament for treating Alzheimer's disease, dementia of the Alzheimer's type, or mild cognitive impairment.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/017439

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/18 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 860 428 A (LILLY CO ELI) 26 August 1998 (1998-08-26) example 51	1-21
X	US 6 166 008 A (ROGERS GARY A ET AL) 26 December 2000 (2000-12-26) column 3, lines 19-37 - column 22, lines 9-15	1-21
X	WO 00/66546 A (CANTRELL BUDDY EUGENE ; FRAY ANDREW HENDLEY (US); JONES WINTON DENNIS) 9 November 2000 (2000-11-09) page 6, line 22 - page 7, line 7; example 11a	1-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 2004	14/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cattell, James

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/017439

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/90057 A (BLEISCH THOMAS JOHN ; CUFF GEORGE WILLIAM (US); LILLY CO ELI (US); ARN) 29 November 2001 (2001-11-29) page 4, lines 18-35	1-21
X	WO 01/90056 A (FRAY ANDREW HENDLEY ; ZARRINMAYEH HAMIDEH (US); LILLY CO ELI (US); AIK) 29 November 2001 (2001-11-29) page 4, lines 18-35	1-21
X	DANYSZ: "Positive modulators of AMPA receptors as potential treatment for schizophrenia" CURRENT OPINION IN INVESTIGATIONAL DRUGS, vol. 3, no. 7, 2002, pages 1062-1066, XP009037522 figure 1	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/017439

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/017439

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